28. **(New)** The method according to claim 13 or 14, wherein said candidate agent is an antisense RNA or DNA, that binds to the nucleic acid encoding said NS5A polypeptide.

B2 cont'd

29. **(New)** The method according to claim 13 or 14, wherein the expression of said PKR protein kinase is inducible.

REMARKS

Claims 1-12 are pending in the present application. A copy of the pending claims, including new claims 13-29 are included in the Appendix attached hereto.

The amendment to the specification is to include a statement that clarifies support and certain rights of the United States Government in the claimed invention, and does not add new matter.

Support for new claims 13-29 can be found throughout the specification, for example, page 6, paragraph 1 to page 7, paragraph 1; page 10 paragraph 1 to page 15, paragraph 1; page 16 paragraph 3 to page 20, paragraph 2; page 45, paragraph 2 to page 48, paragraph 2; and Examples 6-10. Therefore, no new matter is added by way of the addition of new claims 13-29.

In view of the foregoing remarks, Applicant respectfully requests entry of the amendments herein.

Respectfully submitted,
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APPENDIX
(showing pending claims)

1. **(As Filed)** A method for screening for a potential novel agent effective to inhibit the development of malignancies associated with a chronic viral infection, whereby said viral infection is caused by a virus which contains a viral protein with an interferon sensitivity determining region (ISDR), comprising:

incubating a mixture containing PKR protein kinase, the viral protein, and an agent to be tested, and measuring PKR protein kinase activity, comparing to PKR protein kinase activity in the absence of the agent to be tested, and identifying a potential agent by the indication of PKR protein kinase activity in the presence of a test agent.

2. **(As Filed)** The method of Claim 1 wherein the agent inhibits the malignancies associated with chronic hepatitis C viral infection.

3. **(As Filed)** The method of claim 1 wherein the viral protein is NS5A.

4. **(As Filed)** A method of screening for a potential agent effective to inhibit the development of malignancies associated with a chronic viral infection, whereby said viral infection is caused by a virus which contains a viral protein with an interferon sensitivity determining region (ISDR), whereby said agent is effective in inhibiting the direct interaction of an ISDR containing viral protein with an interferon induced PKR kinase, comprising:

incubating a mixture containing the ISDR containing protein, PKR protein kinase and an agent to be tested, and measuring th binding of the ISDR containing protein and the PK protein,
comparing to the degree of binding in the absence of the agent to be tested, and identifying a potential agent by the indication of PKR protein kinase activity in the presence of a test agent.

5. **(As Filed)** The method of Claim 4 wherein the viral protein is NS5A.

6. **(As Filed)** The method of Claim 4 wherein the agent inhibits the malignancies associated with chronic hepatitis C viral infection.

7. **(As Filed)** The method of Claim 1, wherein the PKR protein kinase and the protein containing an ISDR are expressed in a yeast cell genetically engineered to increase expression of a reporter gene in the presence of activated PKR protein kinase, and further comprising measuring the level of expression of the reporter gene in the presence and absence of the agent to be tested.

8. **(As Filed)** The method of Claim 7, wherein the reporter gene product is fused to GCN4/ -gal protein.

9. **(As Filed)** A method for screening for agents comprising a yeast cell which is genetically engineered to express:

(a) a polypeptide containing an ISDR region, and
(b) an interferon-induced PKR protein kinase, and
(c) a reporter gene whose expression is increased in response to activation of the PKR protein kinase, and further comprising measuring the level of expression of the reporter gene in the presence and absence of the agent to be tested.

10. **(As Filed)** The method of Claim 9 wherein the polypeptide containing an ISDR region is NS5A.

11. **(As Filed)** The method of Claim 10 wherein the reporter gene is a fused GCN4/ -gal gene.

12. **(As Filed)** A method of inhibiting the development of malignancies associated with chronic hepatitis C virus (HCV) infection in a cell infected with HCV, comprising administering an effective amount of an agent which interferes with the interaction between NS5A and PKR to said cell, said agent comprising an antisense molecule complementary to the ISDR.

13. **(New)** A method comprising:

a) incubating a reaction mixture comprising
    i) a candidate agent;
    ii) an NS5A polypeptide; and
    iii) a PKR protein kinase polypeptide; and
b) assaying for a difference in a property in the presence of said candidate agent as compared to said property in said reaction mixture incubated in the absence of said candidate agent,

wherein said difference in said property is indicative of the ability of said candidate agent to modulate the interaction of said NS5A polypeptide with said PKR protein kinase polypeptide.

14. **(New)** A method comprising:

a) providing a cell comprising a nucleic acid encoding an NS5A polypeptide and a nucleic acid encoding a PKR protein kinase polypeptide, wherein said NS5A and said PKR protein kinase can be expressed in said cell;
b) introducing into said cell a candidate agent; and
c) assaying for a difference in a property in the presence of said candidate agent as compared to said property in said reaction mixture incubated in the absence of said candidate agent in said cell,

wherein said difference in said property is indicative of the ability of said candidate agent to modulate the interaction of said NS5A polypeptide with said PKR protein kinase polypeptide in said cell.

15. **(New)** The method according to claims 13 or 14, wherein said difference in said property is determined by assaying a decreased level in the binding of said NS5A polypeptide to said PKR protein kinase polypeptide, as compared to the level of binding of said NS5A polypeptide in the absence of said candidate agent, wherein said decreased level in the binding of said NS5A polypeptide to said PKR protein kinase polypeptide is indicative of the ability of said candidate agent to modulate the binding of said NS5A polypeptide to said PKR protein kinase polypeptide.

16. **(New)** The method according to claims 13 or 14, wherein said difference in said property is determined by assaying an increase in the level of dimerization of said PKR protein kinase polypeptide, as compared to the level of dimerization of said PKR protein kinase polypeptide in the absence of said candidate agent, wherein said increase in the level of dimerization of said PKR protein kinase polypeptide is indicative of the ability of said candidate agent to modulate the interaction of said NS5A polypeptide with said PKR protein kinase polypeptide.

17. **(New)** The method according to claims 13 or 14, wherein said difference in said property is determined by assaying an increase in the level of phosphorylation of a substrate as compared to the level of phosphorylation of said substrate in the absence of said candidate agent, wherein said increase in the level of said phosphorylation is indicative of the ability of said candidate agent to modulate the interaction of said NS5A polypeptide with said PKR protein kinase polypeptide.

18. **(New)** The method according to any one of claims 13 or 14, wherein said NS5A polypeptide comprises a portion of the full length NS5A, wherein said portion contains the ISDR.

19. **(New)** The method according to any one of claims 13 or 14, wherein said NS5A polypeptide comprises a portion of the full length NS5A, wherein said portion contains the PKR-binding domain of NS5A.

20. **(New)** The method according to any one of claims 13 or 14, wherein said PKR protein kinase is induced by interferon.

21. **(New)** The method according to any one of claims 13 or 14, wherein said PKR protein kinase polypeptide is selected from a group consisting of p68 kinase, P1, DAI, dsI, and e1F-1 kinase.

22. **(New)** The method according to any one of claims 13 or 14, wherein said PKR protein kinase polypeptide comprises a portion of the full length PKR protein kinase, wherein said portion contains the NS5A-binding domain of said PKR protein kinase.

23. **(New)** The method according to any one of claims 13 or 14, wherein said PKR protein kinase polypeptide further comprises a portion of the full length PKR protein kinase, wherein said portion contains the dimerization domain of said PKR protein kinase.

24. **(New)** The method according to any one of claims 13 or 14, wherein said PKR protein kinase polypeptide comprises a portion of the full length PKR protein, wherein said portion contains the catalytic domain of said PKR protein.

25. **(New)** The method according to any one of claims 13 or 14, wherein said candidate agent is a polypeptide that binds to said NS5A polypeptide.

26. **(New)** The method according to any one of claims 13 or 14, wherein said candidate agent is an antibody that binds to said NS5A polypeptide.

27. **(New)** The method according to claim 13 or 14, wherein said candidate agent is a nucleic acid that binds to the nucleic acid encoding said NS5A polypeptide.

28. **(New)** The method according to claim 13 or 14, wherein said candidate agent is an antisense RNA or DNA, that binds to the nucleic acid encoding said NS5A polypeptide.

29. **(New)** The method according to claim 13 or 14, wherein the expression of said PKR protein kinase is inducible.